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RESEARCH ARTICLE

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A transnational perspective on the evolution of the synthetic cannabinoid receptor agonists market: Comparing prison and general populations

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Abstract

The synthetic cannabinoid receptor agonist (SCRA) market is transnational, and the availability of individual SCRAs changes regularly in response to national and international legislative controls. This generates a cyclic pattern and near constant evolution of SCRA compounds. This study reports toxicology-based and/or seized sample-based prevalence data relating to SCRA use in prisons from Germany, the United Kingdom (UK; Scotland and Wales), and the United States (US), representing 4427 individual test results. The study examines SCRA detections in prisons from July 2018 to September 2020, and where possible, prison-based data are compared with SCRA prevalence data in the wider population. The relative influence of Chinese, other international, and national drug legislation on the prevalence of individual SCRAs in prisons is also considered. *tert*-Leucinate- and valinate-indole- and indazole-3-carboxamides were the most common SCRA detections, and MDMB-4en-PINACA was one of the most commonly detected SCRAs in all jurisdictions by September 2020. However, despite there being a global production and supply market, there were notable regional differences. Analog controls in German and US legislation may have led to increased compound diversity that is not reflected in the UK which has both analog controls and a blanket ban on psychoactive substances. While there were regional differences, SCRA prevalence in prisons closely aligned with the SCRAs detected on the local market, demonstrating that SCRA (and possibly other NPS) monitoring programs in prisons can act as early warning systems for the wider population in that given jurisdiction.

KEYWORDS
4F-MDMB-BINACA, 5F-MDMB-PICA, MDMB-4en-PINACA, prison, synthetic cannabinoid receptor agonists

1 | INTRODUCTION

Synthetic cannabinoid receptor agonists (SCRAs) are a structurally diverse group of new psychoactive substances (NPS) that bind to and activate cannabinoid receptors, CB_1 and CB_2,[1,2] eliciting a range of psychoactive and physiological effects. SCRAs have been implicated in a large number of non-fatal poisonings and drug-related deaths worldwide.[3] Their use and associated harms are of particular concern in vulnerable populations with high incidence of drug use, including those in rough-sleeping communities and prisons or correctional facilities.[4]

Like other NPS markets, the SCRA market is transnational. Technological advances, the use of the internet as a global marketplace, and utilization of international distribution networks have fueled SCRA production and manufacture, primarily based in commercial chemical and pharmaceutical operations in China.[5] SCRAs available for purchase on this global marketplace change regularly in response to changes in legislation. Legislation in producer countries restricts their production and export, and the implementation of national and international legislative controls restricts their import and use in other jurisdictions.[2] This generates a cyclic pattern and constant evolution of new SCRA compounds.

Drug use, and in particular the use of potent NPS, within prison systems poses organizational challenges, leads to significant harms, and requires sustained efforts and resources to address. There is a significant SCRA market in prisons, with 22 European countries reporting their use in this context and concerning use in prisons reported in nine countries including the United Kingdom (UK) and Germany.[4] A recent European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) report on MDMB-4en-PINACA highlighted seizures of this recently emerged SCRA from prisons in six European countries.[6] As a result of their high potency at the CB_1 receptor and their strong psychoactive effects at low doses,[2,7] SCRAs can be infused in active doses into herbal material, paper, clothing, and other materials which are then smoked or vaped.[4] Impregnation of SCRAs into everyday materials, particularly paper and card, makes them much more difficult to detect and allows them to be more effectively supplied to prisoners through mail systems.

The mode of use (e.g., smoking, vaping, and oral) of SCRAs in prisons is generally influenced by whether or not smoking bans are in place. In the United Kingdom, prisons in Wales and Scotland enacted smoking bans in April 2016 and December 2018, respectively, although certain approved e-cigarettes are still allowed for personal use.[8–10] In Germany, smoking is allowed in designated areas, such as in the cell, which is considered a private area.[11] In the United States (US), there are no federal smoking bans for prisons, but many correctional facilities have enacted smoking bans of varying severity, including 100% smoke free indoors and 100% smoke free campuses (indoor and outdoor).[12] In the US state of Pennsylvania, where prison samples reported in this study originated, a tobacco ban was implemented in July 2019, although the use of non-refillable e-cigarettes approved by the prison system is permitted in designated areas.[13] The implementation of smoking bans can drive changes in the mode of use from smoking SCRA-infused herbal blends and rolled up SCRA-infused papers to vaping the SCRA-infused papers and other methods of ingestion (e.g., sublingual and in the eye). The vaping of SCRA-infused papers involves placing small dosage units (typically 1 cm^2) between the heating element and e-liquid cartridge of an e-cigarette.

In order to limit supply, prison authorities can screen incoming mail using ion mobility spectrometers (IMS) and other rapid detection devices,[14,15] as well as by use of drug detection dogs.[16] Laboratory-based seized sample analysis, particularly when aided by in-prison screening with rapid detection devices, can help reduce the supply of drugs in the prisons. Analysis of seized samples also provides information on the specific compounds in circulation, mixtures of compounds being distributed, and the potential concentrations used per dose. The prevalence of SCRAs in correctional establishments can be monitored by urinalysis from drug testing programs; however, since SCRAs are extensively metabolized, and in some cases different SCRAs can produce the same metabolites,[17,18] the exact SCRA compound(s) being used cannot always be unequivocally identified from urinalysis alone.

Close monitoring of market trends and characteristics is important in order to determine the best allocation of resources for disrupting the prison drug market and inform any changes to current policies and security measures.[4,19,20] In addition, accurate data on the prevalence, use, and effects of the drugs are essential in determining the effective management of the problems associated with the drugs, including health risks to individuals using the drugs and the potential safety and security risks the drugs may pose to other prisoners, prison staff, and the prison environment as a whole.[4,19]

This paper reports toxicology-based and/or seized sample-based prevalence datasets relating to SCRA detections in prisons from four geographical regions: Germany, the UK (two distinct datasets from Scotland and Wales), and the United States. The goal was to examine the transnational evolution of the SCRA market in prisons. Where possible, prison SCRA prevalence data were compared with available SCRA prevalence data related to the wider population in the respective jurisdictions. The relative influence of Chinese, other international, and national drug legislation on the prevalence of SCRAs in prisons in a variety of jurisdictions was considered.

2 | METHODS

2.1 | Scotland, United Kingdom

The Leverhulme Research Centre for Forensic Science at the University of Dundee works in partnership with the Scottish Prison Service to analyze non-judicial or non-attributable drug seizures in Scottish prisons. Prevalence data reported in this study originate from 486 seizures from eight prisons between June 2018 and September 2020. Of those, 294 had one or more paper and card samples (visually distinct sets of papers within seizures that are likely of different origin) positive for SCRAs for a total of 388 positive samples. Many of the seizures received for laboratory testing were pre-screened using IMS *in situ* within the prisons and found to have a positive SCRA indication. The qualitative and quantitative screening methods used have been described previously[21,22] and involve qualitative analysis by gas-chromatography-mass spectrometry (GC-MS) and orthogonal confirmation by ultra-performance liquid chromatography with photodiode array and quadrupole time of flight mass spectrometry (UPLC-PDA-QTOF-MS). Selected results for samples seized between June 2018 and February 2020 have been reported previously.[21–23] Additional data from samples seized between October 2019 and September 2020 are presented herein for the first time.

2.2 | Wales, United Kingdom

The Welsh Emerging Drugs and Identification of Novel Substances Project (WEDINOS) is a drug testing service in the United Kingdom operated by Public Health Wales. Prison prevalence data are derived from the analysis of 1152 seized samples, collected from four prisons between July 2018 and June 2020. A total of 316 (27.4%) samples were positive for SCRAs. The prevalence data for the general population come from 373 publicly submitted samples found to contain SCRAs that were received between July 2018 and June 2020. These publicly submitted sample results are available on the WEDINOS website.[24] Analysis was performed on a Waters Acquity I class UHPLC with a Water Xevo G2-XS QTOF-MS (Waters, Elstree, UK). Full details of the analytical method used are provided in Section S1 of the supplementary information.

2.3 | Germany

Prevalence data for 39 German prisons come from the analysis of 2219 urine samples collected between July 2018 and September 2020, of which 745 (33.6%) were positive for SCRAs and SCRA metabolites. Samples were analyzed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) screening method for SCRA metabolites, regularly updated with all relevant compounds and previously published in Franz et al.[25] Prevalence data for the German general population market come from two datasets, one from serum samples and one from infused herbal blends. The serum dataset comes from the analysis of 2539 serum samples, of which 273 (10.8%) were positive for SCRAs. These samples were collected between July 2018 and August 2020 for routine analysis. The majority of these samples were submitted by other forensic laboratories in the context of driving under the influence of drugs offenses. Samples were analyzed with an LC-MS/MS method regularly updated with all relevant compounds and previously published in Giorgetti et al.[26] The infused herbal blends dataset comes from the analysis of 468 SCRA-infused herbal blends, of which 366 (78.2%) were positive for SCRAs. These samples were purchased online, mainly from shops with websites in Germany, as part of a market monitoring program. Herbal blends were analyzed using the method described by Moosmann et al.[27]

2.4 | United States

The Center for Forensic Science Research and Education (CFRSE) partnered with the Pennsylvania Department of Corrections to obtain urine specimens from two prison sites in suburban Philadelphia, PA. Overall, 570 urine samples were collected between March and July 2019. Samples were analyzed using a comprehensive, validated LC-QTOF-MS method described by Krotulski et al.[28] A general population dataset for SCRA use in the United States was obtained from NPS Discovery (a program of CFSRE) based on quarterly trend reports from 2018 Q3 to 2020 Q3.[29] These reports use data from forensic testing of biological fluids, sample extracts, and/or seized drug samples with analysis by GC–MS and LC-QTOF-MS.

2.5 | Preparation of heat map data visualizations

Heat map data visualizations were created in R (version 3.3.1). The datasets used to prepare the heat map data visualizations are provided in the supplementary material (Data S2). An overview of the method to create the heat map visualizations, including a mark-up of the R script, is provided in the supplementary material (Data S1). The R script is provided in the supplementary material (Data S3).

3 | RESULTS AND DISCUSSION

SCRA detections in prisons in Scotland (seizures), Wales (seizures), and Germany (urinalysis) are depicted as heat maps in Figure 1.

3.1 | United Kingdom (Scotland and Wales)

The SCRAs detected in Scottish and Welsh prisons between 2018 Q3 and 2020 Q3 were almost exclusively *tert*-leucinate- and valinate-indole- and indazole-3-carboxamides. In the latest data available for both jurisdictions, MDMB-4en-PINACA and 4F-MDMB-BINACA were the most prevalent SCRAs. 4F-MDMB-BINACA was first

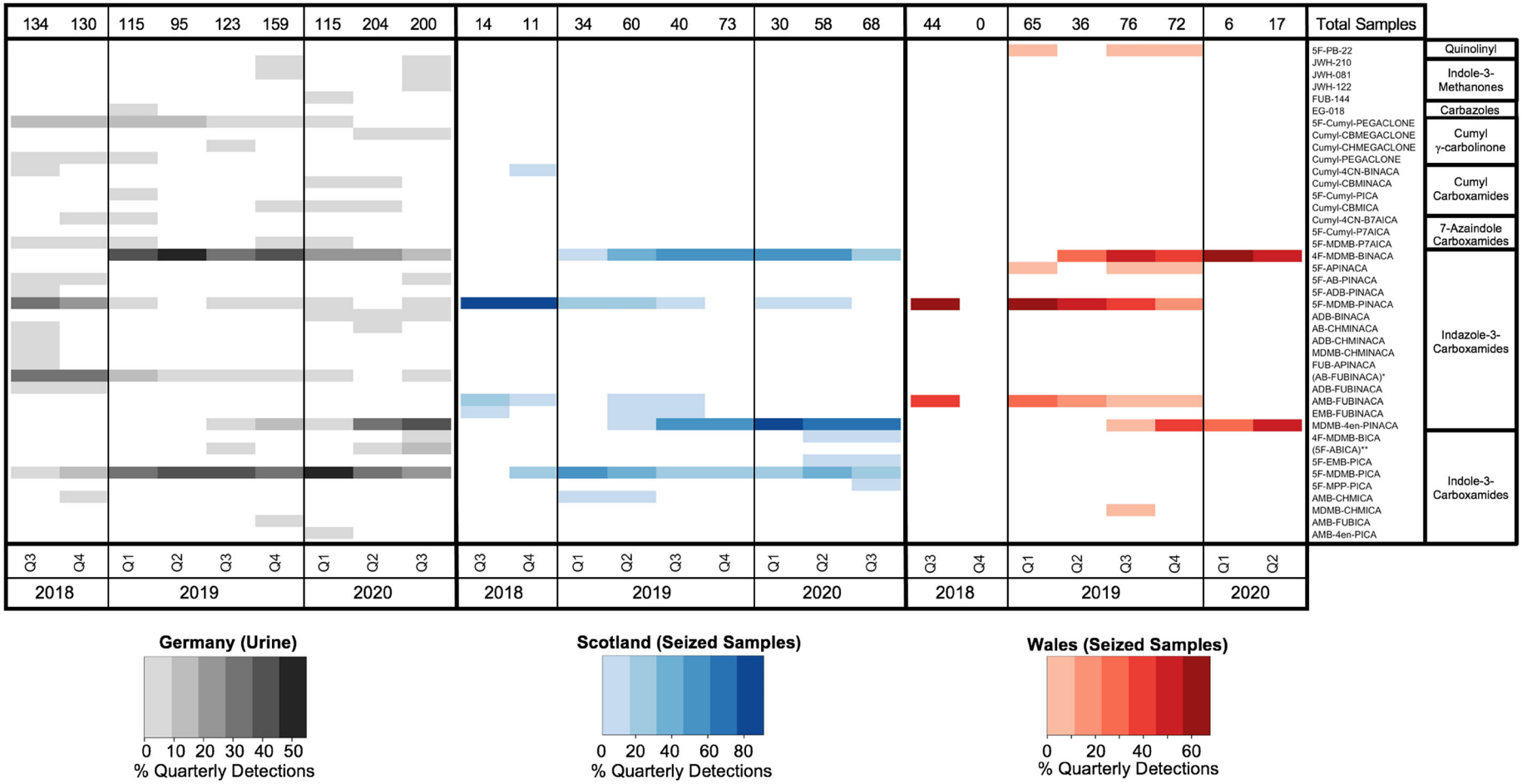

FIGURE 1 Comparison of the synthetic cannabinoid receptor agonist (SCRA) markets in prisons in Germany using toxicological analysis of urine samples and Scotland and Wales using seized sample analysis. Note: SCRA names in parentheses indicate that for the urine analysis (Germany) the amide hydrolysis metabolite of that SCRA was detected, but there are other SCRAs that share the same metabolite. *The AB-FUBINACA amide hydrolysis metabolite could be from AB-FUBINACA, AMB-FUBINACA, or EMB-FUBINACA. **The 5F-ADBICA amide hydrolysis metabolite could be from 5F-ABICA, 5F-AMB-PICA (MMB-2201), or 5F-EMB-PICA

detected in 2019 Q1 in Scottish prisons and 2019 Q2 in Welsh prisons having been first seized in Europe in October 2018.[30] Although it had first been detected in Europe as early as 2017,[6] MDMB-4en-PINACA was first detected in 2019 Q2 in Scottish prisons, becoming the most prevalent SCRA by 2019 Q3. In Welsh prisons, it was first detected in 2019 Q3 and by 2020 Q2 (the last data available) it was as prevalent as 4F-MDMB-BINACA. Emerging SCRAs, 5F-EMB-PICA and 4F-MDMB-BICA, were detected for the first time in Scottish prison seizures in 2020 Q2 having both been first identified in Europe in materials seized by Belgium customs at the end of 2020 Q1.[31–33]

The most notable difference between detections in Scottish and Welsh prisons was that no detections of 5F-MDMB-PICA had been reported in Welsh prisons, despite being one of the most prevalent SCRAs in Scottish prisons over the sampling period. In addition, quinolinyl SCRAs, 5F-PB-22 and 5F-APINACA (5F-AKB-48), were detected in Welsh prisons between 2019 Q1 and 2019 Q4 but were not detected in Scottish prisons at any point during the study period (Figure 1). There were also differences in the type of SCRA-infused materials seized in the prisons between Wales and Scotland. The positive samples in Scotland were exclusively papers, whereas of the SCRA-positive samples in Wales, only 9 (2.8%) were paper, 144 (45.6%) were herbal material, 131 (41.5%) were solid materials, 13 (4.1%) were powder, 2 (0.6%) were e-liquids, and the remaining 17 (5.4%) were "not recorded." This indicates that while the mail system is a primary smuggling route for SCRAs in Scottish prisons, other additional smuggling routes are likely utilized in the Welsh prisons sampled.

In the United Kingdom, SCRAs are controlled as Class B substances under the Misuse of Drugs Act 1971 (MDA 1971) (as amended). Under the MDA 1971, drugs are controlled based on their relative harms into one of three classes, A, B, or C, where Class A drugs are considered the most harmful. Other Class B drugs include cannabis, amphetamine, ketamine, and codeine. SCRAs are listed under structural analog controls which have been adjusted over time to ensure coverage of newly emerging SCRA classes. Any new SCRAs not covered by these analog controls are controlled under the Psychoactive Substances Act 2016 (PSA 2016). This is a blanket ban on the production and supply of all substances for human consumption with psychoactive effects, excluding certain exempt substances. Possession of such substances is not controlled in the general population but is in custodial establishments, such as prisons.[34] All SCRAs detected in Scottish and Welsh prisons are controlled under the MDA 1971 (as amended). There is no legislative reason to explain why 5F-MDMB-PICA is prevalent in Scottish prisons but not in Welsh prisons or why both 5F-PB-22 and 5F-APINACA have continued to be detected in Welsh prisons despite their earlier control in the United Kingdom (December 2016, as part of Order 2016 of the Misuse of Drugs Act 1971),[35] China (October 2015),[36] and internationally (November 2018[37] and March 2017[38], respectively). These variations likely reflect differences in local supply networks and/or use of legacy materials.

Interestingly, as shown in Figure 2, the SCRAs detected in Welsh prisons mirror SCRA detections in samples submitted by the public to the WEDINOS drug testing service, 82.84% of which originated from Wales (15.82% from England and 1.34% from Scotland). Of the publicly submitted samples, 241 (64.6%) were herbal material, 57 (15.3%) were paper, 55 (14.7%) were e-liquids, 13 (3.5%) were crystalline materials, 4 (1.1%) were tablets, and 3 (0.8%) were other solid materials. In publicly forfeited samples, as seen in the prison seizure data, there were no 5F-MDMB-PICA detections, and 5F-PB-22 and 5F-APINACA were still being detected up to 2020 Q2. This indicates that the SCRA prison market is reflective of SCRA prevalence among the national population. No corresponding general population data are

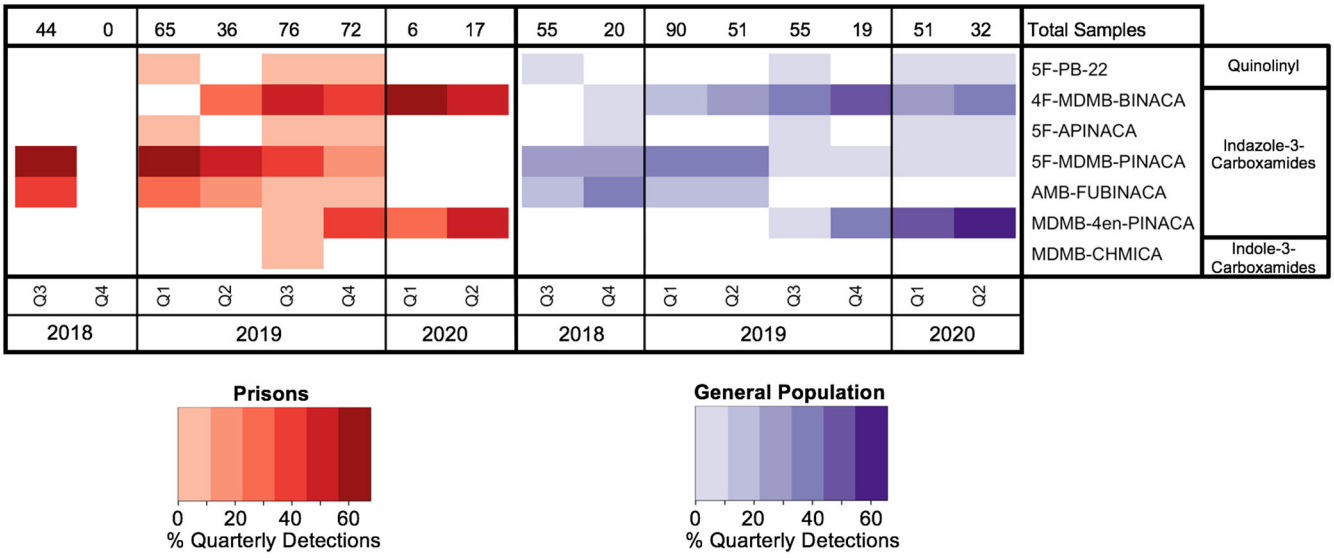

FIGURE 2 Comparison of synthetic cannabinoid receptor agonists (SCRAs) detected in the Welsh prisons versus the WEDINOS general population data (>84% samples originating from Wales) using analysis of seized samples

available for Scotland, but anecdotal information and data from drug-related death statistics suggest that SCRA use occurs almost exclusively in prisons in this region.

3.2 | Germany

Metabolites of the *tert*-leucinate- and valinate-indole- and indazole-3-carboxamides were the most commonly detected substances in urine samples collected from German prisoners. By 2020 Q3, as observed in UK sample seizure data, MDMB-4en-PINACA was the most commonly detected SCRA, having first been detected in 2019 Q3. 4F-MDMB-BICA was first detected in 2020 Q3, whereas it was detected in 2020 Q2 in Scottish prisons, and this SCRA may be increasing in prevalence. It is possible that 5F-EMB-PICA has been detected in German prisons as early as 2020 Q2 as reported in Scottish prisons, because the 5F-ABICA amide hydrolysis metabolite, which is a metabolite of 5F-EMB-PICA, was detected; however, since it is also a metabolite of 5F-ABICA and 5F-AMB-PICA (MMB-2201/5F-MMB-PICA), the exact parent SCRA compound could not be determined solely from the urinalysis. It is notable that the SCRAs and/or SCRA metabolites detected in German urine samples are considerably more structurally diverse than in the UK seized samples. In particular, SCRAs incorporating a cumyl head group and/or a γ-carbolinone core structure are more prevalent in Germany than in the United Kingdom or the United States and several naphthoylindole SCRA (e.g., JWH-210) metabolites were detected in urine samples as recently as 2020 Q3 (Figure 1). The diversity of SCRA detections in the prison urinalysis reflects the greater diversity in the general population SCRA market as determined by analysis of seized and test-purchased materials and serum samples (Figure 3). The greater diversity observed in the German populations could be due to the larger sample sizes in the prison urinalysis data and general population serum data than the other jurisdictions; however, the German purchased sample dataset shows much the same variation despite a smaller sample size.

Since the enactment of legislation covering NPS (NpSG = Neue-psychoaktive-Stoffe-Gesetz) in November 2016, Germany now implements analog controls for SCRAs as described in detail in previous publications.[39,40] When first enacted, the legislation controlled 86% of the SCRAs monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA), including the most prevalent SCRAs on the market at that time.[39] However, the legislation appears, at least in its early phases, to have driven SCRA diversity in the German domestic market with compounds appearing to be specifically designed to avoid legislative control via the NpSG. These include SCRAs with a γ-carbolinone core structure (e.g., 5F-Cumyl-PEGACLONE), azaindoles (e.g., 5F-MDMB-P7AICA), and carbazoles (e.g., MDMB-CHMCZCA). While these compounds were not prevalent within the other jurisdictions in this paper, they have been found to be prevalent in other jurisdictions outside Germany, such as Cumyl-CHMEGACLONE which was first reported in Hungary in December 2018 and showed significant prevalence.[41] Legislative changes to cover SCRAs with increasingly diverse core structures were enacted via the NpSG in July 2019, and these cover the γ-carbolinone substances. This may have led to a greater diversification of the tail structures producing, for example, the recently detected Cumyl-CBMICA, an indole-3-carboxamide SCRA with a cyclobutyl methyl tail.[40]

3.3 | United States

As far as the authors are aware, there is no formal monitoring or data collection process in place for monitoring the prevalence and use of SCRAs in correctional institutions in the United States. The goal of the sub-study was to test prison populations to determine the extent of SCRA use in a single geographical location within the United States. Of the 570 urine samples tested, 14 samples (2.4%) were positive for SCRA metabolites: 11 (1.9%) were positive for 5F-MDMB-PICA 3,3-dimethylbutanoic acid and 3 (0.5%) for 4F-MDMB-BINACA 3,3-dimethylbutanoic acid. Drug positivity rates reported by the Pennsylvania Department of Corrections between October 2018 and September 2019 ranged between 0.3% and 0.9%.[42] The increase in positivity among those testing positive for SCRAs could be explained by the use of a comprehensive testing methodology and a regularly updated library database (i.e., testing for more appropriate drugs based on current and emerging trends). For example, 4F-MDMB-BINACA was the newest SCRA to emerge around the time of testing and incorporation of this analyte into the database yielded positive results that would otherwise be missed without vigorous and novel protocols.

Within the US general population SCRA market, as shown in Figure 4 based on the data from NPS Discovery trend reports,[29] 4F-MDMB-BINACA was first detected in December 2018.[43] Quickly, 4F-MDMB-BINACA became the second most prevalent SCRA in the United States behind 5F-MDMB-PICA in 2019 Q1. Data show that 4F-MDMB-BINACA began having widespread implications among forensic toxicology casework, including medicolegal death investigations, often in combination with 5F-MDMB-PICA early on.[44] Interestingly, in the prison population study, the metabolite of 4F-MDMB-BINACA was detected in urine samples as early as March 2019. This suggests that the drug markets leading to overdose deaths at least overlap with the drug markets fueling SCRA use in prisons and also shows the quick emergence of new SCRAs within the prison system just a short time (or immediately) after their emergence in the general population.

The US general population data from NPS Discovery demonstrate similar trends and emergence timelines as the National Forensic Laboratory Information System (NFLIS, a program of the Drug Enforcement Administration) data.[45] A heat map comparison of the two datasets can be found in Figure S3.1 of the supplementary information. NFLIS data come from the analysis of seized drug samples by federal, state, and local laboratories throughout the United States, in comparison to NPS Discovery, which in addition utilizes biological fluids analysis data. The emergence of new SCRAs appears to be

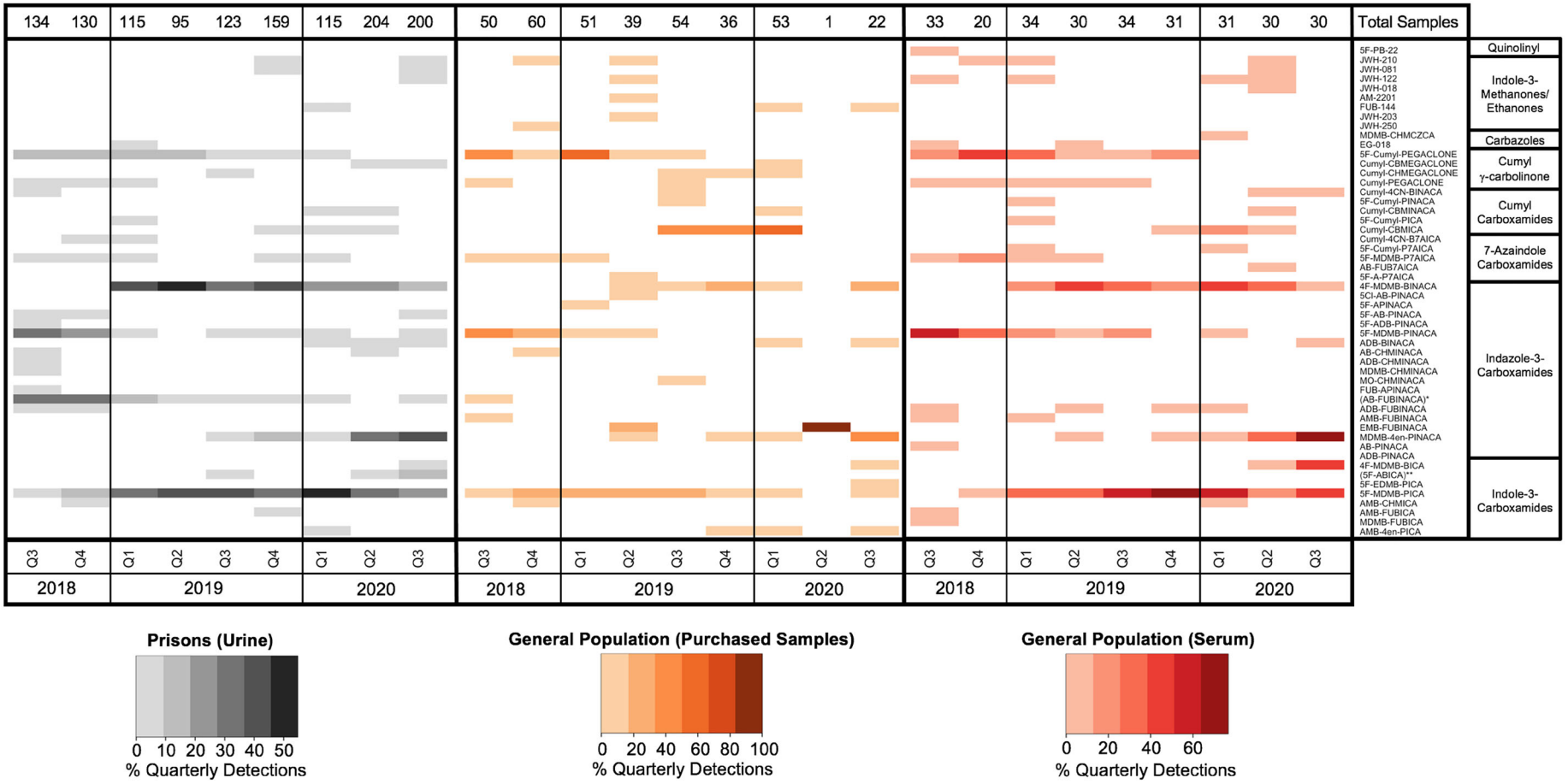

FIGURE 3 Comparison of synthetic cannabinoid receptor agonists (SCRAs) detected in the German prisons using toxicological analysis of urine samples versus the German general population from SCRA-infused herbal blends purchased online and analysis of serum samples. Note: SCRA names in parentheses indicate that for the urine analysis (Germany) the amide hydrolysis metabolite of that SCRA was detected, but there are other SCRAs that share the same metabolite. *The AB-FUBINACA amide hydrolysis metabolite could be from AB-FUBINACA, AMB-FUBINACA, or EMB-FUBINACA. **The 5F-ADBICA amide hydrolysis metabolite could be from 5F-ABICA, 5F-AMB-PICA (MMB-2201), or 5F-EMB-PICA

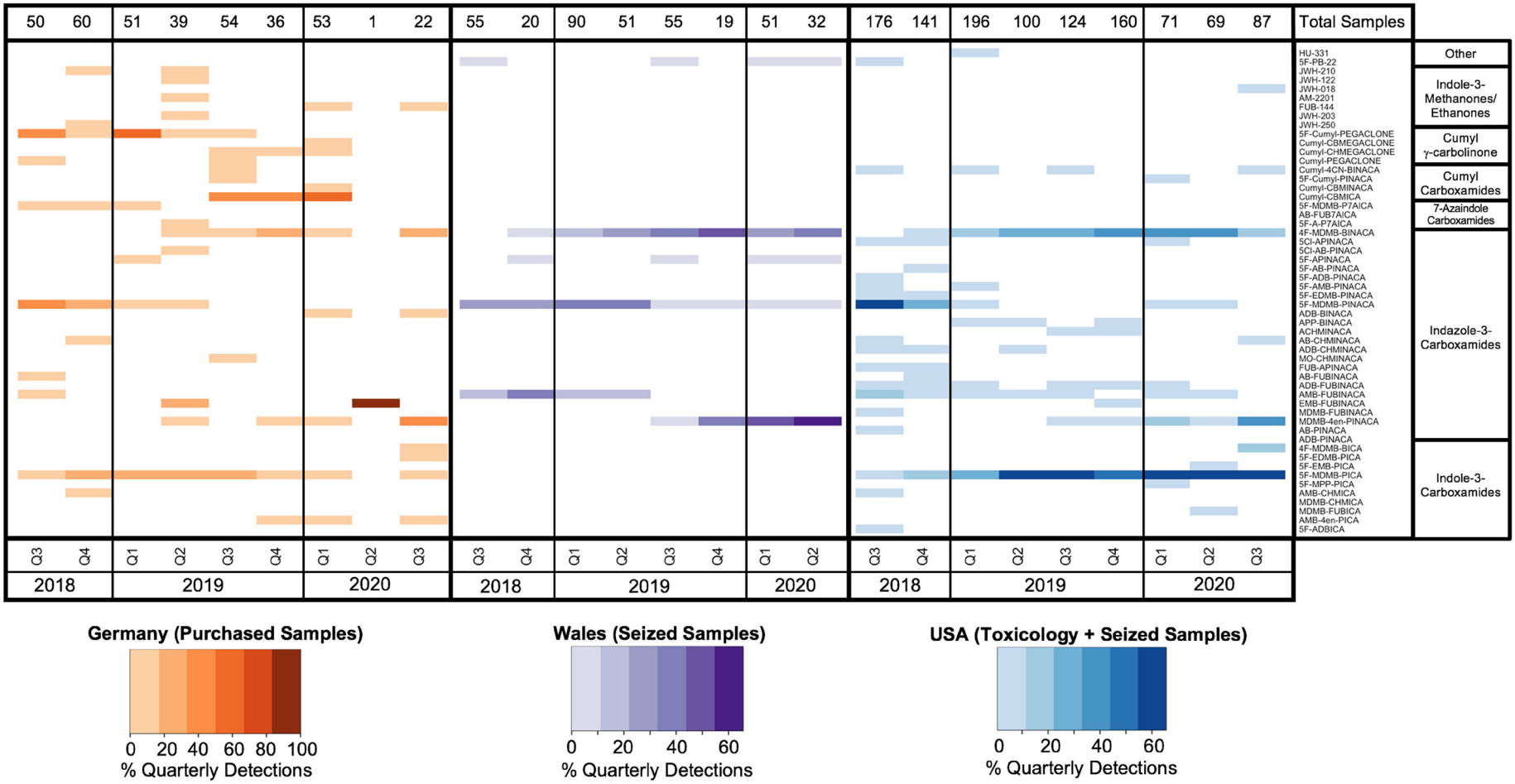

FIGURE 4 Comparison of the synthetic cannabinoid receptor agonist (SCRA) markets in the general population in Germany from SCRA-infused herbal blends purchased online, Wales using seized sample analysis, and the United States, based on data from the new psychoactive substance (NPS) Discovery trend reports, using toxicological analysis of urine samples and seized sample analysis

similar between NPS Discovery and NFLIS; although since NFLIS typically only report their SCRA detections in mid-year and annual reports, the first emergence of a SCRA compound can be more difficult to determine using this dataset. 4F-MDMB-BINACA was first detected in the 2018 annual report, not the mid-year report, indicating that NFLIS also had first detections of 4F-MDMB-BINACA in 2018 Q3 or Q4. On the other hand, they reported detections of MDMB-4en-PINACA in the 2019 mid-year report, indicating detections in 2019 Q1 or Q2, whereas NPS Discovery had first detections in 2019 Q3. In addition, NPS Discovery seems to have more variation in their SCRA detections than NFLIS; however, NFLIS do not report the exhaustive list of SCRAs detected but include an "other synthetic cannabinoids" category that constitutes between 16.63% and 19.77% of SCRA detections.

The United States uses both individual drug scheduling actions and analog controls for SCRAs through the temporary or permanent scheduling of compounds plus their isomers under Schedule I of the Controlled Substances Act (CSA).[46] The definition of an isomer, both optical and positional, is provided in Title 21 of the Code of Federal Regulations (CFR).[47] 5F-MDMB-PICA was temporarily scheduled on 28 December 2018,[48] the same month that 4F-MDMB-BINACA was first detected in the general population samples. 4F-MDMB-BINACA is treated as a "positional isomer" of 5F-AMB-PINACA (5F-AMB; 5F-MMB-PINACA), which was scheduled on 10 April 2017,[49] and therefore does not require separate scheduling action. It is unknown whether this was obvious to SCRA producers who *may* have been trying to circumvent US legislation.

3.4 | Legislative changes as a driver of SCRA prison market diversification

International and national legislation is clearly a significant driver for diversification of the SCRAs detected in prisons (and SCRA availability in the general population) at both local and global levels. Such legislative changes can be classified as (i) national actions in producer/exporter jurisdictions directly affecting availability on the global SCRA market; (ii) changes made to international legislation via the World Health Organization (WHO) Expert Committee on Drugs and Drug Dependence (ECDD), which often highlights drugs to be considered for control up to a year in advance as part of a critical review process; and (iii) national legislation in jurisdictions into which SCRAs are imported and consumed (e.g., MDA 1971 in the United Kingdom, NpSG in Germany, and CSA in the United States).

Legislation controlling SCRA production and export in SCRA-producing countries, such as China, seems to have the greatest influence on the availability of compounds worldwide.[50] When new SCRAs emerge in response to legislative changes in China, they tend to do so in a global manner and previously prevalent substances tend to leave the market relatively quickly. For example, it was determined that the August 2018 ban of eight SCRAs by China, including the two most prevalent SCRAs at the time, AMB-FUBINACA (AMB-FUB, FUB-AMB), and 5F-MDMB-PINACA (5F-ADB), resulted in these SCRAs rapidly disappearing from illicit markets in Scotland, Germany, and New Zealand,[21,39,51] as well as Wales (Figure 2) and the United States (Figure 4) as shown herein by the data presented. 5F-MDMB-PICA appeared on the market soon after. 5F-MDMB-PICA had originally been detected in 2016 but had disappeared from the market in 2017.[52] Its re-emergence was reported in the German prison and serum general population datasets (Figure 3) and in the United States in 2018 Q3 (Figure 4) and in Scottish prisons in 2018 Q4 (Figure 1). This was followed by 4F-MDMB-BINACA, with first reports in Europe and the United States in 2018 Q4 (October[30] and December, respectively). 4F-MDMB-BINACA was then detected in Scottish and German prisons in 2019 Q1 and Welsh prisons in 2019 Q2. The emergence of 4F-MDMB-BINACA may have been in response to the temporary scheduling of 5F-MDMB-PICA in the United States in December 2018, which demonstrates that local legislative changes may perhaps, on occasion, have an effect at a global level, although no causal link has been established.

In October 2019, the WHO ECDD indicated that 5F-MDMB-PICA and 4F-MDMB-BINACA were under review for consideration for international control with the legislation coming into force on 3 November 2020.[6,53] The increasing prevalence of MDMB-4en-PINACA in the United Kingdom, Germany, and the United States from 2019 Q2 onwards may have been a pre-emptive response to this, although MDMB-4en-PINACA was detected in Europe as early as 2017.[54,55] MDMB-4en-PINACA is now the most commonly detected SCRA in Scottish prisons and in Germany as a whole and is the second most prevalent SCRA detected in the United States and Wales as of 2020 Q2. Recently reported data from 2020 Q4 from NPS Discovery show that MDMB-4en-PINACA is now the most commonly detected SCRA in the United States.[56] MDMB-4en-PINACA is now being considered forinternational control at both the European and global level by EMCDDA and WHO ECDD, respectively.[6,54] If recommended for control at a global level by WHO ECDD, the control may not come into force until November 2021. The emergence of 4F-MDMB-BICA and 5F-EMB-PICA on the drug market in 2020 Q2 may therefore again be a pre-emptive market response to the control of 5F-MDMB-PICA and 4F-MDMB-BINACA and also, possibly, to the future international control of MDMB-4en-PINACA.

While the emergence of prevalent SCRAs is very similar across all jurisdictions, being influenced by legislation in producer countries and international controls, national legislation can also drive increased diversity in local markets as well as international markets. There is relatively little diversity in the SCRA market in prisons in the United Kingdom with a limited number of compounds being detected at any given time, all with similarly high potency and efficacy, where pharmacological information is available.[23,57] Since the current UK legislation covers the most prevalent SCRAs on the market under analog controls (MDA 1971) and all other SCRAs that may not be covered under the PSA 2016, the United Kingdom may no longer be a driver of market diversification at a local or international level. In contrast, the analog controls in Germany (NpSG) and the United States (CSA) appear to have led to increased diversity in the local market that does not

appear to be reflected in other jurisdictions (i.e., γ-carbolinone SCRAs are rarely seen in the United Kingdom and United States).

There are some interesting regional differences that cannot be explained by legislation. For example, WEDINOS has never detected 5F-MDMB-PICA despite it being one of the most commonly detected SCRAs in the other jurisdictions and worldwide for, in some places, more than a year. This demonstrates that market evolution is complex and while legislation can be an important driver for SCRA market change, there are other variables that can influence the availability of a specific compound in a particular jurisdiction (e.g., trafficking routes, local supply networks, user interest/reports, and adverse effects).

4 | CONCLUSION

SCRAs detected in prisons closely align with the SCRAs detected on the local market, but there are regional differences despite a global market for production and supply. This finding is significant and critically important for combating the emergence and proliferation of SCRAs in the future. This transnational study demonstrates that SCRA (and possibly other NPS) monitoring programs in prisons can act as early warning systems for the wider population in that given jurisdiction. Such monitoring programs should, where possible, be near real-time and should inform the application of detection methodologies designed to limit SCRA supply into prisons to ensure their effectiveness and ability to reduce harm. Where urinalysis is deployed for the testing of urine samples collected from prison populations and where targeted detection methods are employed, it is imperative that those methods are kept up to date with relevant testing panels by incorporating new SCRAs reported nationally and internationally. A laboratory must constantly monitor changing drug trends, especially for NPS and particularly for SCRAs, and incorporate new drugs into testing methodologies as rapidly as possible; otherwise, positive results within the population could be missed and drug use could be wrongly counted or categorized.

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CONFLICT OF INTEREST

The authors do not report any conflicts of interest.

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REFERENCES

1. Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol*. 2006;147(S1):S163-S171. https://doi.org/10.1038/sj.bjp.0706406
2. Banister SD, Connor M. The chemistry and pharmacology of synthetic cannabinoid receptor agonists as new psychoactive substances: origins. In: Maurer HH, Brandt SD, eds. *Handbook of Experimental Pharmacology 252: New Psychoactive Substances*. Cham, Switzerland: Springer Nature Switzerland AG; 2018:165-190.
3. Giorgetti A, Busardò FP, Tittarelli R, Auwärter V, Giorgetti R. Post-mortem toxicology: a systematic review of death cases involving synthetic cannabinoid receptor agonists. *Front Psych*. 2020;11:1-22. https://doi.org/10.3389/fpsyt.2020.00464
4. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *New Psychoactive Substances in Prison: Results From an EMCDDA Trendspotter Study*. Luxembourg: Publications Office of the European Union; 2018.
5. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Fentanils and Synthetic Cannabinoids: Driving Greater Complexity Into the Drug Situation*. Luxembourg: Publications Office of the European Union; 2018.
6. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EMCDDA initial report on the new psychoactive substance methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate (MDMB-4en-PINACA). 2020. https://www.emcdda.europa.eu/system/files/publications/13363/emcdda-initial-report-MDMB-4en-PINACA.pdf Accessed November 23, 2020.
7. Banister SD, Connor M. The chemistry and pharmacology of synthetic cannabinoid receptor agonists as new psychoactive substances: evolution. In: Maurer HH, Brandt SD, eds. *Handbook of Experimental Pharmacology 252: New Psychoactive Substances*. Cham, Switzerland: Springer Nature Switzerland AG; 2018:191-226.
8. McCarthy J. This is what will happen when smoking is banned in Welsh prisons, according to a charity. *Wales Online* April 2, 2016. https://www.walesonline.co.uk/news/wales-news/what-happen-smoking-banned-welsh-11122931 Accessed September 3, 2020.
9. Alderson R. Prisoners to be offered free vaping kits ahead of tobacco ban. *BBC Scotland* August 29, 2018. https://www.bbc.co.uk/news/uk-scotland-45333234 Accessed November 1, 2018.
10. BBC News. Parc prison: rise in violence since smoking ban. July 20, 2017. https://www.bbc.co.uk/news/uk-wales-south-east-wales-40657742 Accessed September 3, 2020.
11. Baybutt M, Ritter C, Stöver H. Tobacco use in prison settings: a need for policy implementation. In: Enggist S, Møller L, Galea G, Udesen C, eds. *Prisons and Health*. Copenhagen: World Health Organization Regional Office for Europe; 2014:138-147.
12. Zhang J. Prison smoking bans in the United States: Current policy, impact and obstacle. *J Hosp Manag Health Policy*. 2018;2(5):1-4. https://doi.org/10.21037/jhmhp.2018.04.06
13. Pennsylvania Pressroom. Department of Corrections facilities to be tobacco free by July 1. https://www.media.pa.gov/Pages/corrections_details.aspx?newsid=392 Accessed November 9, 2020.
14. Bell V, Leese M. A Mixed Methods Study of Increased Security Measures in a Drug Recovery Prison: Final Report May 2019. https://research.tees.ac.uk/ws/portalfiles/portal/8490384/DRP_security_measures_final_draft_report.pdf Accessed January 27, 2020.

15. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *New Psychoactives Substances in Europe. An Update From the EU Early Warning System March 2015*. Luxembourg: Publications Office of the European Union; 2015.
16. Ford LT, Berg JD. Analytical evidence to show letters impregnated with novel psychoactive substances are a means of getting drugs to inmates within the UK prison service. *Ann Clin Biochem*. 2018;55(6): 673-678. https://doi.org/10.1177/0004563218767462
17. Watanabe S, Kuzhiumparambil U, Nguyen MA, Cameron J, Fu S. Metabolic profile of synthetic cannabinoids 5F-PB-22, PB-22, XLR-11 and UR-144 by Cunninghamella elegans. *AAPS J*. 2017;19(4): 1148-1162.
18. Carlier J, Diao X, Scheidweiler KB, Huestis MA. Distinguishing intake of new synthetic cannabinoids ADB-PINACA and 5F-ADB-PINACA with human hepatocyte metabolites and high-resolution mass spectrometry. *Clin Chem*. 2017;63(5):1008-1021. https://doi.org/10.1373/clinchem.2016.267575
19. Public Health England. New psychoactive substances (NPS) in prisons: A toolkit for prison staff. 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/669541/9011-phe-nps-toolkit-update-final.pdf Accessed September 25, 2019.
20. Djemil H. *Inside Out: How to Get Drugs Out of Prisons*. London, UK: Centre for Policy Studies; 2008. https://www.cps.org.uk/files/reports/original/111026174106-INSIDEOUT.pdf Accessed September 25, 2019.
21. Norman C, Walker G, McKirdy B, et al. Detection and quantitation of synthetic cannabinoid receptor agonists in infused papers from prisons in a constantly evolving illicit market. *Drug Test Anal*. 2020;12(4):538-554. https://doi.org/10.1002/dta.2767
22. Norman C, McKirdy B, Walker G, Dugard P, Nic Daéid N, McKenzie C. Large-scale evaluation of ion mobility spectrometry for the rapid detection of synthetic cannabinoid receptor agonists in infused papers in prisons. *Drug Test Anal*. 2020. https://doi.org/10.1002/dta.2945
23. Antonides LH, Cannaert A, Norman C, et al. Shape matters: the application of activity-based in vitro bioassays and chiral profiling to the pharmacological evaluation of synthetic cannabinoid receptor agonists in drug-infused papers seized in prisons. *Drug Test Anal*. 2020. https://doi.org/10.1002/dta.2965
24. Welsh Emerging Drugs and Identification of Novel Substances. Sample Results. https://www.wedinos.org/db/samples Accessed November 23, 2020.
25. Franz F, Angerer V, Jechle H, et al. Immunoassay screening in urine for synthetic cannabinoids—an evaluation of the diagnostic efficiency. *Clin Chem Lab Med*. 2017;55(9):1375-1384. https://doi.org/10.1515/cclm-2016-0831
26. Giorgetti A, Mogler L, Haschimi B, et al. Detection and phase I metabolism of the 7-azaindole-derived synthetic cannabinoid 5F-AB-P7AICA including a preliminary pharmacokinetic evaluation. *Drug Test Anal*. 2020;12(1):78-91. https://doi.org/10.1002/dta.2692
27. Moosmann B, Kneisel S, Girreser U, Brecht V, Westphal F, Auwärter V. Separation and structural characterization of the synthetic cannabinoids JWH-412 and 1-(5-fluoropentyl)-1H-indol-3yl-(4-methylnaphthalen-1-yl)methanone using GC-MS, NMR analysis and a flash chromatography system. *Forensic Sci Int*. 2012;220(1–3): e17-e22. https://doi.org/10.1016/j.forsciint.2011.12.010
28. Krotulski AJ, Mohr ALA, Logan BK. Emerging synthetic cannabinoids: Development and validation of a novel liquid chromatography quadrupole time-of-flight mass spectrometry assay for real-time detection. *J Anal Toxicol*. 2020;44(3):207-217. https://doi.org/10.1093/jat/bkz084
29. NPS Discovery. Trend reports. https://www.npsdiscovery.org/reports/trend-reports Accessed November 23, 2020.
30. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EU Early Warning System Briefing. [Spread of 4F-MDMB-BINACA in Europe.] EU-EWS-RCS-BR-2019-0002. 04 04 2019.
31. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EU Early Warning System Formal Notification. [Notification of 5F-EMB-PICA in Europe.] EU-EWS-RCS-FN-2020-0020.
32. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EMCDDA Initial Report on the New Psychoactive Substance methyl 2-({[1-(4-fluorobutyl)-1H-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate (4F-MDMB-BICA). 2020. https://www.emcdda.europa.eu/system/files/publications/13362/emcdda-initial-report-4F-MDMB-BICA.pdf Accessed November 23, 2020.
33. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EMCDDA Technical Report on the New Psychoactive Substance methyl 2-{[1-(4-fluorobutyl)-1H-indole-3-carbonyl]amino}-3,3-dimethylbutanoate (4F-MDMB-BICA). 2020. https://www.emcdda.europa.eu/system/files/publications/13477/TR-4F-MDMB-BICA_Advanced-release.pdf Accessed January 12, 2021.
34. UK Home Office. Review of the Psychoactive Substances Act 2016. 2018. https://www.gov.uk/government/publications/review-of-the-psychoactive-substances-act-2016 Accessed June 30, 2020.
35. United Kingdom Government. The Misuse of Drugs Act 1971 (Amendment) (England, Wales, and Scotland) Regulations 2016 (S.I. 2016/1109). http://www.legislation.gov.uk/uksi/2016/1109/pdfs/uksiem_20161109_en.pdf Accessed November 23, 2020.
36. United Nations Office on Drugs and Crime (UNODC). October 2015 - China: China announces controls over 116 new psychoactive substances. https://www.unodc.org/LSS/Announcement/Details/83b02e73-4896-4ed5-944c-51a7646647aa Accessed May 18, 2020.
37. United Nations Office on Drugs and Crime (UNODC). November 2018 - UNODC: Commission on narcotic drugs decision on international control of 4-fluoramphetamine (4-FA), AB-PINACA, AB-CHMINACA, 5F-PB-22, UR-144, and 5F-MDMB-PINACA (5F-ADB) enters into force. https://www.unodc.org/LSS/Announcement/Details/2a0dd30f-c322-4f89-bd4d-90a0e5196314 Accessed October 26, 2020.
38. United Nations Office on Drugs and Crime (UNODC). Inclusion of 5F-APINACA (5F-AKB-48) in Schedule II of the Convention on Psychotropic Substances of 1971. https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_60/CNDdec_2017/Decision_60_10_60CND.pdf Accessed October 26, 2020.
39. Halter S, Haschimi B, Mogler L, Auwärter V. Impact of legislation on NPS markets in Germany—the rise and fall of 5F-ADB. *Drug Test Anal*. 2020;12(6):1-4. https://doi.org/10.1002/dta.2786
40. Halter S, Pulver B, Wilde M, et al. Cumyl-CBMICA: a new synthetic cannabinoid receptor agonist containing a cyclobutyl methyl side chain. *Drug Test Anal*. 2020;13(1):208-216. https://doi.org/10.1002/dta.2942
41. Haschimi B, Giorgetti A, Mogler L, et al. The novel psychoactive substance Cumyl-CH-MEGACLONE: human phase-I metabolism, basic pharmacological characterization and comparison to other synthetic cannabinoid receptor agonists with a γ-carboline-1-one core. *J Anal Toxicol*. 2020. https://doi.org/10.1093/jat/bkaa065
42. Pennsylvania Deparment of Corrections. Drug interdiction performance measures. https://www.cor.pa.gov/AboutUs/Statistics/Documents/Reports/Drug-Interdiction-Indicators.pdf Accessed December 3, 2020.
43. NMS Labs. 4F-MDMB-BINACA Monograph. https://www.npsdiscovery.org/wp-content/uploads/2019/05/4F-MDMB-BINACA_011118_NMSLabs_Report.pdf Accessed November 23, 2020.
44. NPS Discovery. New Synthetic Cannabinoid: 4F-MDMB-BINACA. 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/06/Public-Alert_4F-MDMB-BINACA_NPS-Discovery_013119.pdf Accessed November 23, 2020.

45. National Forensic Laboratory Information System (NFLIS). NFLIS Published Reports. https://www.nflis.deadiversion.usdoj.gov/Reports.aspx Accessed January 12, 2020.
46. United States Government. Title 21 United States Code (USC) Controlled Substances Act. https://www.deadiversion.usdoj.gov/21cfr/21usc/ Accessed November 9, 2020.
47. United States Food and Drug Administration. Code of Federal Regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm Accessed November 9, 2020.
48. United States Department of Justice. Schedules of Controlled Substances: Temporary Placement of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA, and FUB-144 in Schedule I. 2018. https://www.deadiversion.usdoj.gov/fed_regs/rules/2018/fr1228_2.htm Accessed November 9, 2020.
49. U.S. Drug Enforcement Administration. 4F-MDMB-BINACA (4F-MDMB-BUTINACA). 2019. https://www.deadiversion.usdoj.gov/drug_chem_info/4F-MDMB-BINACA.pdf Accessed November 9, 2020.
50. Seddon T. Drug policy and global regulatory capitalism: the case of new psychoactive substances (NPS). *Int J Drug Policy*. 2014;25(5):1019-1024. https://doi.org/10.1016/j.drugpo.2014.03.009
51. Stansfield CR, Somerville RF, Hassan VR, et al. Effects of external influences on synthetic cannabinoid trends in New Zealand, 2014 to 2020. *Forensic Sci Int*. 2020;316(110485):1-6. https://doi.org/10.1016/j.forsciint.2020.110485
52. Expert Committee on Drug Dependence (ECDD). Critical Review Report: 5F-MDMB-PICA. Geneva: World Health Organization; 2019. https://www.who.int/medicines/access/controlled-substances/Final_5F-MDMB-PICA.PDF?ua=1 Accessed December 3, 2020.
53. United Nations Office on Drugs and Crime (UNODC). October 2019 - WHO: NPS to be Reviewed for Potential Scheduling Under the International Drug Control Conventions. https://www.unodc.org/LSS/Announcement/Details/16221a5d-8f88-4975-b41f-8eb4327e8fe0 Accessed November 23, 2020.
54. Expert Committee on Drug Dependence (ECDD). Critical Review Report: MDMB-4en-PINACA. Geneva: World Health Organization; 2020. https://www.who.int/docs/default-source/controlled-substances/43rd-ecdd/mdmb-4en-pinaca-review-2020.pdf?sfvrsn=5cd6e97e_4 Accessed November 23, 2020.
55. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). EMCDDA technical report on the new psychoactive substance methyl 3,3-dimethyl-2-{[1-(pent-4-en-1-yl)-1H-indazole-3-carbonyl]amino}butanoate (MDMB-4en-PINACA). 2020. https://www.emcdda.europa.eu/system/files/publications/13478/TR-MDMB-4en-PINACA_Advanced-release.pdf Accessed January 12, 2021.
56. NPS Discovery. Trend Report: Q4 2020. 2020. https://www.npsdiscovery.org/wp-content/uploads/2021/01/2020-Q4_Synthetic-Cannabinoids_Trend-Report.pdf Accessed January 13, 2021.
57. Antonides LH, Cannaert A, Norman C, et al. Enantiospecific synthesis, chiral separation, and biological activity of four indazole-3-carboxamide-type synthetic cannabinoid receptor agonists and their detection in seized drug samples. *Front Chem*. 2019;7:1-20. https://doi.org/10.3389/fchem.2019.00321

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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